***Highlights (for review)**

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1. Freezing behavior in Parkinson's disease occurs in both gait and non-gait domains.
2. Freezing elicited during non-gait paradigms is similar to gait freezing.
3. Motor-cognitive triggers of non-gait freezing fit well with conceptual models of FOG.
4. Freezing is likely related to impairments in frontostriatal neural communication.

Title: Freezing beyond gait in Parkinson's disease: a review of current neurobehavioral evidence

Running title: Freezing phenomena in PD

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Abstract (170/170 words)

Besides the continuous motor impairments that characterize Parkinson's disease (PD), patients are frequently troubled by sudden paroxysmal arrests or brief episodes of movement breakdown, referred to as 'freezing'. Freezing of gait (FOG) is common in advanced PD and typically occurs in walking conditions that challenge dynamic motor-cognitive control. Mounting evidence suggests that episodic motor phenomena during repetitive upper limb (e.g. writing), lower limb (e.g. foot tapping) and speech sequences resemble FOG and may share some underlying neural mechanisms. However, the precise association between gait and non-gait freezing phenomena remains controversial. This review aimed to clarify this association based on literature on non-gait freezing published between 2000 and 2013. We focused on clinical and epidemiological features of the episodes and their relevance to current influential models of FOG, including recent neuroimaging studies that used a non-gait freezing paradigm as a proxy for FOG. Although not capturing the full complexity of FOG, the neurobehavioral insights obtained with non-gait freezing paradigms will contribute to an increased understanding of disturbed brain-behavior output in PD.

Key words

Parkinson's disease, freezing of gait, freezing, upper limb, lower limb, speech, motor block, festination, neuroimaging, basal ganglia.

Highlights

1. Freezing behavior in Parkinson's disease occurs in both gait and non-gait domains.
2. Freezing elicited during non-gait paradigms is similar to gait freezing.
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Contents

1. Introduction

Parkinsonian motor disturbance is characterized by spatiotemporal control deficits such as bradykinesia, hypokinesia, dysrhythmicity and impaired bilateral coordination (Jankovic, 2008). This clinical pattern is especially observed when patients perform repetitive, sequential movements that recruit motor processes through the dysfunctional basal ganglia and manifest themselves in many daily activities such as walking, writing and speaking. Regarding locomotor control, Giladi and colleagues (2013) emphasized the distinction between continuous gait impairments that consistently affect the gait pattern, and episodic phenomena that are transient and unpredictable. Freezing of Gait (FOG) is without doubt the best described type of episodic movement breakdown and is defined as a '*brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk*' (Nutt et al., 2011). During a FOG episode, patients suddenly stop involuntarily as if their feet are glued to the floor. FOG negatively impacts on mobility, falls and quality of life (Moore et al., 2007; Kerr et al., 2010). Kinematic analysis of lower limb segments during a FOG episode, showed highly abnormal rather than completely absent movement patterns, which differentiates the episode from continuous abnormalities, voluntary stops and fatigue (Bloem et al., 2004; Hausdorff et al., 2003; Nieuwboer et al., 2001; Schaafsma et al., 2003).

FOG research has largely been driven by two important approaches. Firstly, although FOG is a common gait disorder (Macht et al., 2007), it does not affect all patients equally, suggesting that the comparison of patients with FOG (PD+FOG) and patients without FOG (PD-FOG) may aid in the search for neurobehavioral markers of the symptom. Secondly, patients typically freeze in response to increased motor, cognitive and limbic load, such that triggers of FOG have been extensively investigated (Nutt et al., 2011; Nieuwboer and Giladi, 2013). These insights have catalyzed the development of a number of topical papers that have linked FOG to a combination of exaggerated motor impairments (see Plotnik et al., 2012 and Heremans et al., 2013a for review) and reduced cognitive resources that involve executive functioning (see Heremans et al., 2013b; Shine et al., 2013d and Vandenbossche et al., 2012 for review).

Giladi et al. (1992) proposed the general term 'motor blocks' for the episodic motor phenomena inherent to PD, irrespective of the type of movement and the effectors involved. Early studies reported that finger tapping provokes 'manual motor blocks' (Ziv et al., 1999) and 'finger festination' (Nagasaki et al., 1996), which showed correlations with patients' gait abnormalities. Similarly, Ackermann et al. (1993) provided circumstantial evidence for 'speech freezing' in one akinetic-rigid patient who demonstrated abnormally fast speech repetitions with reduced articulatory amplitude during an oral diadochokinetic task. Since then, the number of publications on episodic phenomena during repetitive upper limb, lower limb and speech motor control has continued to increase. Moreover, these non-gait freezing phenomena are currently being used as proxies for freezing of gait in neuroimaging experiments, as directly studying walking itself is not possible in a scanning environment (Shine et al., 2013a, 2013b, 2013c; Vercruysse et al., 2013). However, the overlap between clinical and epidemiological characteristics of non-gait freezing problems and FOG is still a matter of debate. In addition, it is currently unclear whether the recent motor-cognitive models that explain the emergence of breakdown during gait (see Nieuwboer and Giladi, 2013 for review), translate to similar breakdowns in motor control that is not associated with gait.

1.2 Aim and scope of the review

The primary aim of this review was to critically examine the link between FOG and non-gait freezing phenomena based on literature published between January 2000 and October 2013. We will therefore describe and illustrate episodic phenomena in studies that examined motor control involving the lower limbs (section 2.1), upper limbs (section 2.2) and speech (section 2.3) in patients with Parkinson's disease. We specifically discuss their clinical manifestation, the behavioral constraints that triggered the episode and the kinematic properties during the episode, which we will highlight in overview figures. In addition, we report the evidence pro or contra the co-occurrence of non-gait freezing and FOG within patients. The parallels between lower limb, upper limb and speech freezing are then combined (section 2.4) in order to explore their relevance to current conceptual models of FOG (Nieuwboer and Giladi, 2013).

As a secondary aim, we summarized the results of recent neuroimaging studies that adopted a non-gait freezing motor paradigm to unravel the brain mechanisms related to episodic breakdown in PD (section 3). The novel insights will be discussed against a background of core involvement of basal ganglia networks in regulating sequential motor tasks and in dynamically integrating motor-cognitive processes.

Finally, the last section (section 4) provides tentative conclusions regarding the evidence and relevance of non-gait freezing in relation to FOG.

2. Current evidence on non-gait freezing

In the upcoming paragraphs, we outline the main characteristics of episodic motor phenomena that were described in PD patients during the performance of experimental or functional tasks involving the lower limbs (but not gait), upper limbs and speech control. We used PubMed to search for literature of which the title and/or abstract made mention of an episodic failure termed 'motor block(s)', 'motor arrest(s)', 'hesitation', 'freezing', 'freezing of gait', 'gait freezing', 'akinesia/akinetic', 'festination' or 'movement breakdown' in combination with one of the search terms covering the types of movement under investigation ('upper limb', 'lower limb', 'hand(s)', 'finger(s)', 'feet/ foot', 'stepping' or 'articulation/articulatory', 'oral', or 'speech'). Next, articles were screened for relevance based on their abstract and main text. Other relevant references cited by these papers were also explored. After exclusion of 1) papers not written in English, 2) review articles, 3) studies on continuous motor deficits without description of an episodic event and 4) articles published before January 1st 2000, 33 articles were maintained (nine on lower limb phenomena, 17 on upper limb phenomena, four on speech disturbances and two on more than one type of non-gait freezing).

2.1. Episodic motor phenomena in lower limb movements

Insert **Table 1** about here
Descriptive overview of episodic phenomena during lower limb movements

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Insert **Table 2** about here
Illustrative overview of episodic phenomena during lower limb movements

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Table 1 summarizes the evidence on episodic motor phenomena during lower limb movements in PD patients. Abe et al. (2003) investigated rotational velocity waveforms in order to assess inter-limb coordination deficits during semi-passive pedaling movements in PD and control subjects. The bicycle

ergometer allowed for uncoupled pedaling of left and right legs. The authors found that whereas healthy subjects oscillated the rotational velocities of the right and left pedals with almost constant amplitude and relative phase at 180°, PD patients exhibited varied characteristics of rotational velocities. Interestingly, only the patients that experienced discontinuous changes in rotational velocity (e.g. abnormal coordination patterns with sudden cessations followed by re-initiation of pedaling (see Table 2(A) for illustration)) were considered as having 'the freezing phenomenon'. The freezing phenomenon was referred to by the authors as a "motor block" where the initiation or continuation of a motor act is arrested for a few seconds. However, it is unclear how the presence of FOG was established and if the number or durations of lower limb cessations observed in this study varied with FOG severity. In addition, it remains unclear whether the sudden cessations observed in this study are indeed freezing like phenomena or rather represent intentional stops in order to reestablish a preferred relative phase of motion.

In another study, rhythmic stepping in place (SIP) task at comfortable pace elicited freezing episodes defined as the inability to lift the foot from the force plate, in 13 of 15 patients with self-reported FOG (Nantel et al., 2011). As illustrated in Table 2(B), Nantel and colleagues demarcated the event on the basis of vertical forces. The authors implemented this objective criterion in a computerized algorithm in a second study (Nantel et al., 2012, Table 2(C)). Both studies evidenced a higher occurrence of freezing episodes in patients with FOG compared to those without. Lower limb freezing could predict the presence of FOG and was correlated to the FOG-Questionnaire (FOG-Q). Moreover, stepping movements of patients with FOG were more asymmetric and more variable in timing than in non-freezing counterparts. SIP performance also correlated to specific visuospatial deficits, rather than with executive dysfunction in general (Nantel et al., 2012).

Based on visual inspection of cyclic foot movements, Vercruysse et al**.** (2012a) reported freezing episodes in 73% of patients with FOG whereas no such events were observed in non-freezers. Lower limb freezing included both complete arrests as well as periods of nearly complete loss of movement. Patients were lying in supine while moving the feet in an alternating pattern at comfortable speed. The number of trials with lower limb freezing was moderately correlated to FOG severity measured by the FOG-Q (r=0.59), but not with disease severity.

The occurrence of freezing episodes during functional movements of the lower limbs was assessed using a non-gait freezing questionnaire (Vercruysse et al., 2012b). Fifty-seven percent of patients with confirmed FOG and eight % of patients without FOG reported motor blocks, associated with the feeling of having their feet glued to the floor, when wiping their feet. The composite non-gait freezing score (including items of upper limb and speech freezing as well) contributed to the prediction of FOG in this sample. However, future validation of this questionnaire is warranted.

In a series of experiments, Lewis and colleagues described freezing-like motor arrests during pedaling foot movements, which participants made in order to advance in a virtual reality walkway (Gilat et al., 2013; Matar et al., 2013; Shine et al., 2013e). Motor arrests (also termed 'freezing episodes') during the VR task were defined when the temporal gap between two alternating 'footsteps' exceeded twice the patient's modal footstep latency. The accelerometer traces of foot movements during the freezing episodes as shown in Table 2(D) indicate typical trembling in place and a good recovery of footsteps cadence following an arrest (unpublished data). Gilat et al. (2013) also showed increased step time variability in the five steps leading up to a freeze. In all studies, freezing episodes occurred more frequently and with longer duration in patients with FOG, independent of the level of

motor-cognitive load imbedded in the VR experiment. In Gilat et al. (2013), freezers' off-medication performance on the VR task was characterized by increased step time variability and spontaneous motor arrests. Matar et al. (2013) compared larger groups of freezers and non-freezers while on medication. Patient groups were not matched for disease severity but had similar UPDRS foot tapping scores. Footstep latencies were triggered by increased visuomotor load delivered by narrow and sliding doorways in the virtual walkway and by cognitive interference due to incongruent color-word cues to stop or continue walking. VR freezing in response to these triggers was correlated to FOG-Q score (r=0.28-0.32). These results were partially replicated in confirmed freezers who showed longer and over twice the amount of VR freezing episodes compared to non-freezers when tested off medication (Shine et al., 2013e). In this study, VR freezing was not associated with higher self-reported FOG (FOG-Q) but, importantly, correlated to the occurrence of FOG during a functional gait task (timed up and go test (TUG), r=0.51).

In summary, all eight reviewed papers support the idea that episodic motor breakdown during bilateral lower limb motor tasks is more frequent in PD with compared to without FOG. Furthermore, these phenomena were all correlated with FOG severity, either as assessed by the FOG-Q (Nantel et al., 2011; 2012; Vercruysse et al., 2012; Matar et al., 2013), by gait analysis (Shine et al., 2013a) or in predicting a freezer/non-freezer classification (Nantel et al., 2011; 2012; Vercruysse et al., 2012). Except for the VR motor-cognitive interference that may probe mechanisms of complex gait control (Gilat et al., 2013; Matar et al., 2013; Shine et al., 2013e), most studies reported on the spontaneous occurrence of freezing episodes. This relates to 'open-runway' FOG, i.e. freezing in the absence of clear external triggers which is in fact a rather rare form of FOG. From a methodological standpoint, future studies should seek to clarify the role of volitional decision processes in the emergence of motor arrests (Abe et al., 2003) and would benefit from more rigorous or validated tools to assess freezing (Vercruysse et al., 2012a; 2012c). In addition, the effect of external cueing on preventing freezing episodes in these tasks has not been addressed so far and would be relevant for daily activities in which patients reported freezing (Vercruysse et al., 2012c).

2.2. Episodic motor phenomena in upper limb movements

Insert **Table 3** about here
Descriptive overview of episodic phenomena during upper limb movements

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Insert **Table 4** about here
Illustrative overview of episodic phenomena during upper limb movements

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The current evidence on episodic motor phenomena during upper limb movements in PD and their graphical illustrations are presented in Table 3 and Table 4. Using a digitized keyboard, Bronte-Stewart et al. (2000) recorded velocity and frequency profiles during unilateral, alternating finger tapping of adjacent fingers in 16 PD patients and 11 controls. The PD patients in their study showed marked difficulties with the timing of motor sequences that could be improved by dopaminergic medication uptake. Some patients demonstrated freezing (Table 4(A)), either during ongoing movement or just after the start command ('start akinesia'). A 'freeze' denoted an epoch of complete cessation of movement in one or both fingers that exceeded the average inter-finger tapping interval

of the preceding 5 seconds by at least two standard deviations. Although gait deficits were not reported in this test sample, the authors interpreted upper limb freezing, and more specifically, the preceding festinating behavior, as potentially related to FOG. The quantitative digitography method also allowed to objectively distinguish freezing from other clinical phenomena such as fatigue, bradykinesia and tremor.

Almeida et al. (2002) compared the performance of optimally medicated PD patients and controls on a bimanual task involving large (16 cm) sliding movements of two blocks on a surface with both hands moving towards the midline (in-phase coordination) or one moving away and one towards the midline (anti-phase coordination). Patients demonstrated greater spatiotemporal deficits during anti-phase trials as compared to controls, with little improvement by auditory cues. In eight percent of anti-phase trials, patients showed upper limb 'freezing episodes' (at least one second breaks) which could also have represented voluntary stops to correct phasing errors (Table 4(B)). Freezing was considered distinct from hypometric events which were characterized by a sustained reduction in amplitude for 5 seconds (five percent of anti-phase trials). In a second experiment (Almeida et al., 2003), motor-cognitive load was increased in the bimanual task by asking subjects to switch from one coordination pattern to the other in response to an auditory tone. Switching to the more difficult anti-phase pattern triggered freezing episodes in 54% of PD trials compared to 16% of trials that required a switch to in-phase movements. Freezing could affect one or both hands (Table 4(C)). Delayed motor responses upon hearing the cue, possibly indicating initiation freezing, were present in 3.4% of in- to anti-phase switching trials (vs. 1.7% in the reverse pattern). These studies did not examine the frequency of upper limb freezing in patients with and without FOG as separate groups.

Yahalom et al. (2004) described the group performance of a unimanual tapping task as 'hastened' in tremor-dominant and freezing-dominant PD when their tapping frequency was significantly higher compared to control subjects. They found more hastening in conditions in which a metronome imposed a high frequency and, surprisingly, more so in the tremor- versus freezing-dominant subtype. In tremor-dominant patients, an abrupt switch in movement frequency provoked more hastening than a stepwise speed increase. The authors acknowledged that using average group rather than individual changes in the kinematic signal may have disregarded brief periods of hastening in either group.

Rhythmic thumb movements at maximal speed and amplitude (+/- 2 cm) were examined in 15 PD and 6 healthy controls (Sauermann et al., 2005). Subjects had to press a button with the thumb of their dominant and non-dominant hand separately. A small group of patients (2.5%) demonstrated hand akinesia or 'hesitations' which correlated to UPDRS III hand coordination items 24 and 25. Hesitations, also called 'short instances of standstill', were detected when the thumb extension or flexion was interrupted (Table 4(D)). The authors made no references to FOG.

In a study focused on oral festination in PD, Moreau et al. (2007) also addressed upper limb motor performance in 31 patients with and nine patients without FOG/festination. Patients performed a bilateral finger tapping task at their comfortable pace while off medication. It was found that episodes of hastening and motor blocks were more frequent in PD patients who also experienced festination and freezing of gait.

Popovic et al. (2008) tested the clinical validity of a digitizer tablet in detecting motor blocks in rhythmic hand movements during a seven-day period. Eight patients, on their usual medication, performed large (>20 cm) unilateral point-to-point movements without further motor constraints.

Motor blocks were defined as a time interval with no change in coordinates along the X and Y axis (Table 4(E)). Three patients demonstrated motor blocks, accounting for 12% of all PD trials. Importantly, the 3 patients with motor blocks also showed severe impairment on item 24 of the UPDRS III (hand movements), including initiation problems and motor arrests. Patients without motor blocks all scored less than 3 on this item. Gait characteristics were not reported.

A similar tablet was used by Nieuwboer et al. (2009) to examine the relation between freezing during bimanual alternating writing movements and FOG. The bimanual task was executed at two levels of movement amplitude (4 cm and 2 cm) and speed (comfortable and fast). The majority of patients with FOG (70%) showed upper limb freezing defined as periods without movement in one or both hands preceded by scaling and timing abnormalities (see Table 4 (F)). In these subjects, UL freezing severity was correlated to the FOG-Q total score. In contrast, only one subject in the PD-FOG group showed upper limb freezing. Interestingly however, this subject developed FOG a few months later. Overall, patients with FOG did not show more pronounced spatiotemporal difficulties during movement without freezing compared to their non-freezing counterparts, unlike earlier descriptions of freezers' gait pattern (Hausdorff et al., 2003; Plotnik et al., 2005; 2008; Iansek et al., 2006; Nieuwboer et al., 2007). Although, patients with FOG responded less to visual cueing, suggesting reduced ability to compensate for disturbed motor control in this group.

Stegemöller et al. (2009) described a frequency-induced movement breakdown during unilateral finger tapping in PD patients with clinically determined akinetic rigidity in the upper limbs (UPDRS scores on items 33-25 ≥ 2). In contrast to controls, patients responded with a dramatic decrease in amplitude and increase in frequency when a cued pace was set above 2 Hz (Table 4(G)). Electromyography showed that this was due to a failure to increase agonist muscle activity of the first dorsal interosseous (FDI) beyond 2 Hz, rather than to co-contraction of agonist and antagonists muscles. Similarly, FOG was associated with an altered timing of leg muscles without losing the loss of reciprocal coordination (Nieuwboer et al., 2004). Stegemöller and colleagues suggested that the observed breakdown could contribute to motor arrests in finger and hand movements but no association with FOG was made. Moreover, medication intake did not improve performance or muscle activity, questioning the sole contribution of deficient processing through basal ganglia circuitries.

The VR paradigm used to evaluate repetitive foot movements in response to doorways and cognitive interference as described in the above section was previously validated using the upper limbs (Naismith et al., 2010). Subjects were asked to tap their hands in an alternating way in order to navigate in a virtual walkway. In PD patients on medication, this 'hand-controlled stepping' elicited start hesitations and freezing episodes. Both examples of delayed motor output correlated to patients' FOG severity (r=0.59 and r=0.58 respectively), suggesting shared underlying mechanisms.

To our knowledge, the only study on episodic motor disturbances in recently diagnosed patients was performed by Jones et al. (2011). Subjects made repetitive finger taps in a synchronization-continuation paradigm with four inter-tap-intervals. It was found that movement accuracy depended on whether patients had started dopaminergic treatment or not. Treated patients tended to move ahead of the beat, especially after the auditory cue was withdrawn (continuation phase). This hastened behavior was in contrast to the motor slowness of the untreated group. These results suggest that motor festination can be worsened by dopaminergic medication, an idea that is in line

with the dose-dependent severity of both upper limb and gait freezing after levodopa intake in patients with paradoxical ON-state FOG (Espay et al., 2012).

Three other studies used a similar synchronization-continuation paradigm as Jones et al., to directly compare finger tapping performance in patient groups with and without FOG (Vercruysse et al. 2012a; 2012c, Williams et al., 2013). By means of objective spatiotemporal criteria, Vercruysse et al. (2012a) detected freezing episodes (Table 4(H)), defined as 'periods of involuntary stops or clear absence of effective cyclic movement' in 82% of PD with FOG compared to 17% of PD without FOG irrespective of disease severity. Further associations with FOG were found in that, similar to known triggers of FOG, upper limb freezing was mostly triggered by alternating movements at maximal speed and reduced amplitude and that upper limb severity correlated to FOG severity. However, this correlation could not be replicated by using a similar paradigm in a fMRI context where 56% versus 6% of patients with and without FOG showed upper limb freezing (Vercruysse et al., 2013). An important finding was that kinematic properties of upper limb freezing, namely the sequence effect prior to the episode and abnormally high-frequency, and the trembling-like output during the freeze resembled those of FOG (Hausdorff et al., 2003, Nieuwboer et al., 2001; Schaafsma et al., 2003). Spatiotemporal impairments appeared persistent in PD with FOG when examining time series outside of freezing episodes (Vercruysse et al., 2012c). Williams et al. (2013) corroborate these results, by showing that upper limb freezing (Table 4(I)) tended to be more common in PD with compared to without FOG and was associated with continuous scaling, timing and coordination deficits, especially in finger tapping conditions that required fast and small movements. Both episodic as well as continuous deficits were correlated to FOG severity. As mentioned in the above section, a summed score of non-gait freezing during functional motor tasks was found to be a predictor of FOG (Vercruysse et al., 2012b). For tasks involving the upper limbs, freezing during writing was reported by 30% of PD with FOG and six percent of patients without FOG.

Taken together, the reviewed studies clearly evidence episodic phenomena in various unilateral and bilateral upper limb tasks. These events were either characterized by a nearly-complete loss of movement and abnormal scaling and timing output or, less frequently, by complete arrests at movement initiation (Bronte-Stewart et al., 2000; Almeida et al., 2003; Naismith et al., 2010). The phenomena were mostly elicited by motor constraints although the additional influence of a secondary cognitive task (Almeida et al., 2003; Naismith et al., 2010) merits further attention, especially when considering upper limb functioning in daily life (Vercruysse et al., 2012c). In several cases, the relation with FOG was left unexplored possibly because upper limb movements are less intuitively connected to gait (Almeida et al., 2002; 2003; Sauermann et al., 2005; Popovic et al., 2008; Stegemöller et al., 2009; Jones et al., 2011; Stegemöller et al., 2013). When systematically addressed, the evidence in favour of co-occurrence (Moreau et al., 2007; Nieuwboer et al., 2009; Espay et al., 2012; Vercruysse et al., 2012a; 2012b; 2012c; Williams et al., 2013), correlated severity (Nieuwboer et al., 2009; Vercruysse et al., 2012a; 2012b; 2012c; Williams et al., 2013) and shared background or episodic spatiotemporal dynamics (Vercruysse et al., 2012a; 2012b; 2012c; Williams et al., 2013) seems to be stronger than the single study that contradicted an association between upper limb and gait freezing (Yahalom et al., 2004).

2.3. Episodic motor phenomena in speech

Insert **Table 5** about here
Descriptive overview of episodic phenomena during speech

Table 5 summarizes the five papers on speech freezing or related speech abnormalities in PD. No graphical illustrations were available. In the DATATOP study of Giladi et al. (2001), freezing of gait and UPDRS (speech) scores were prospectively assessed in 800 early PD patients. Speech control was scored by means of item 5 of the ADL section and item 1 of the motor section of the UPDRS. Speech impairment was present in 1.9% of patients at baseline and was associated with developing FOG longitudinally. According to the authors, some of the impairments reflected FOG-like problems in repetitive motor control, namely problems with repeating the first syllables of a word (palilalia), hastened speech (tachyphemia) and speech pauses or vocal arrests (speech freezing). Word finding difficulties such as the tip-of-the-tongue phenomenon may reflect 'cognitive freezing' which we envisage as a temporary block in processing or retrieving stored information, but this remains to be investigated.

Moreau et al. (2007) compared the performance of a syllable repetition task in PD with and without freezing and/or festination of gait focusing on the temporal dissociation between the imposed frequency (IF, 1-7Hz) and executed frequency (EF). They identified periods of oral festination when the EF exceeded patients' mean control EF in at least one IF condition. Oral festination was present in 45% of PD patients in general and in 70% of patients with combined gait freezing and festination. Isolated FOG (without clear festination) was associated with a sudden breakdown in the EF, possibly reflecting speech freezing.

Cantaniaux et al. (2010) found that the way PD patients read a text out loud was related to both spatial and temporal features of gait control as measured during straight-line walking. Both tasks were performed at comfortable, slow and maximal speeds. Speech akinesia, characterized by clear reductions in the inter-pause interval, was proposed as the main speech impairment in PD. Speech akinesia and other timing difficulties were correlated to reduced step length and gait arhythmicity. Moreover, both gait and speech timing improved in conditions ON medication and ON deep brain stimulation (DBS) of the STN.

Subjective reports of speech freezing as an item of the non-gait freezing questionnaire were made by 44% of patients with confirmed FOG compared to 13% of patients without FOG (Vercruysse et al., 2012b). A higher incidence of freezing-like dysfluencies was also reported by Park et al. (2013). In that study, subjects read 10 sentences out loud, either in the presence or absence of visual and auditory cues. Visual cues were presented as arrows that moved at a fixed, slow pace from one syllable to the next, similar to the temporal guidance of auditory tones. In addition, articulatory complexity was manipulated by using mono- or polysyllabic words. The number of syllable or word repetitions per sentence served to measure speech dysfluency. Patients also performed standardized gait tests in both conditions with and without visual or auditory cues. In contrast to the group of PD without FOG, a correlation was found between the beneficial effects of cueing on speech and gait performance in PD with FOG.

To summarize, the described evidence supports a general association between spatiotemporal deficits in speech and gait control and suggests that improvement can be reached through medical (Cantiniaux et al., 2010) and rehabilitation interventions (Park et al., 2013). Further evidence was

provided by the predictive value of speech freezing in FOG development (Giladi et al., 2001; Vercruysse et al., 2012c) and their co-occurrence within patients (Moreau et al., 2007). However, the concept of speech freezing is more complex because of the occurrence of different speech phenomena (e.g. oral festination, palilalia etc.) and the lack of kinematic analysis (Giladi et al., 2001; Vercruysse et al., 2012c). Cognitive problems are likely to play a role in sudden speech disruptions, possibly by aggravating a central 'block' in information processing.

2.4. Are all types of freezing the same?

Overall, the evidence encourages a distinction between continuous and episodic motor disturbances in research on lower limb, upper limb and speech control in PD, similar to what Giladi and colleagues proposed for locomotion (Giladi et al., 2013). Clinically, the 3 types of non-gait freezing phenomena mostly emerged in response to motor constraints, either experimentally manipulated by different levels of spatiotemporal load or inherently embedded in maintaining a sequential movement pattern (spontaneous freezing). Yet not all repetitive movements elicit freezing equally. Movements that are small in amplitude were shown to run a higher risk of hastening and freezing. In addition, bilateral tasks may be more sensitive to freezing when left and right motor sequences are uncoupled, in keeping with the preserved ability to cycle as on a regular bike, even in the case of severe FOG (Snijders and Bloem, 2010). Cognitive load in the form of dual task interference and behavioural switching proved to elicit freezing in the lower (Matar et al., 2013; Shine et al., 2013e) and upper limbs (Almeida et al., 2003) but was not investigated in the context of speech. Breakdown after some time of movement generation was more frequently reported than at movement initiation in all effectors.

Kinematically, it appears that all of the episodic phenomena shared specific features such as a decreased amplitude, increased frequency, increased variability and asymmetry and decreased inter-limb coordination, however sometimes manifested as a complete absence of movement altogether. Scaling-timing abnormalities in the cycles preceding the freeze were shown in lower limb (Gilat et al., 2013) and upper limb studies (Vercruysse et al., 2012a). However, the above observations must be interpreted with caution as the profoundly different methodologies and measurements employed in the studies do not allow for direct comparisons to be made. As such, future studies are encouraged to investigate different types of non-gait freezing within subjects whilst utilizing the same paradigms and objective criteria to define freezing. So far, only two attempts were made in this perspective, showing correlated occurrence of lower limb, upper limb and speech freezing and a joint predictive effect in FOG development (Vercruysse et al., 2012a; 2012c). Epidemiological information reviewed here also provided strong evidence for co-occurrence of FOG and non-gait freezing within patients.

Similar to FOG (Nutt et al., 2011), cueing modalities were found to both provoke and alleviate non-gait freezing symptoms depending on the situation. Indeed, visual and auditory cueing have an overall positive effect on upper limb kinematics in freezers (Nieuwboer et al., 2009; Vercruysse et al., 2012a), whilst visual salient features have been shown to trigger lower limb freezing (Matar et al., 2013). Moreover, lower limb motor paradigms and locomotion in particular can be accompanied with a continuous updating of visual information as the scene changes. This is not the case for upper limb movements. As such, future research may benefit from investigating the effect of visual information on both upper and lower limb freezing.

2.5. Relevance for conceptual models of FOG

Nieuwboer and Giladi (2013) recently proposed four models of different but possibly interacting motor and cognitive mechanisms leading to FOG. Each model yields a testable prediction of daily situations or experimental manipulations that would enhance the risk for FOG. Here, we briefly summarize how the insights on non-gait freezing relate to these models, as indicated in the right columns of Table 1, 3 and 5.

1) In the *threshold model* (Plotnik et al., 2012), FOG occurs as a result of the simultaneous deterioration of multiple gait features (e.g. stride length, stride timing, bilateral coordination) such that the compound walking pattern is pushed below an imaginary threshold of movement breakdown. Motor constraints including smaller step length, faster movement frequency and more complex bilateral coordination such as turning, are viewed as crucial triggers of FOG.
   The current evidence that non-gait freezing is mostly triggered by motor constraints and to some extent, related to continuous motor disturbances, is in keeping with this model. The threshold model may be of use to study the emergence of lower limb, upper limb and speech freezing in future research.
2) The *interference model* is built on a neural reserve hypothesis (Lewis and Barker, 2009) assuming that FOG is induced by the competing neural processing of motor, cognitive and limbic information. The model concurs with patients freezing in stressful situations for example, when trying to reach a ringing telephone or in complex conditions where gait is to be combined with a secondary task. Similarly, we found that dual task situations elicited lower and upper limb freezing suggesting that the interference model is applicable to movement breakdown in other effectors as well.
3) In the *cognitive model* (Vandenbossche et al., 2012), FOG reflects a behavioral indecision towards one of conflicting responses. Patients with executive dysfunction and impaired response inhibition would be especially prone to experience FOG when dealing with incongruent stimuli while walking. The secondary task added to the VR stepping and hand tapping consisted of incongruent word-color cues to stop or continue moving. It is also possible that other non-gait freezing studies using cues to switch from one type of behavior to another (e.g. from simultaneous to alternating movements, or from externally to internally generated movements) prompted cognitive processes that provoke movement breakdown.
4) Last, the *decoupling model* (Jacobs et al., 2009) views FOG as the delay or failure in automatic generation of a movement pattern when it mismatches a preparatory motor program. This model best explains FOG at gait initiation and takes into account the worsening effect of postural instability. The lower limb freezing episodes on the SIP task which heavily depended on weight shifting (Nantel et al., 2011; 2012) support this model. The first-person perspective video of a person walking in the VR paradigm (Gilat et al., 2013; Matar et al., 2013; Shine et al., 2013e), either controlled by stepping or tapping movements, could have induced internal postural representations as well but this needs further testing. As mentioned above, initiation freezes also appeared during non-gait motor paradigms but were less frequent than freezing during ongoing movement.

3. Neural mechanisms of non-gait freezing in PD and their relation to FOG

Two important commonalities of freezing phenomena point to a core involvement of basal ganglia (BG) pathways. First, freezing occurred in movement tasks that have a sequential or repetitive structure. Sequential movements highly depend on BG-cortical interaction because they require the correct implementation and the automatic running of movement amplitude and frequency. PD impairs these spatiotemporal aspects, resulting in hypokinetic movements which may become progressively smaller (the sequence effect) and faster (hastening) with ongoing performance. In line with the threshold model (Plotnik et al., 2012), Iansek and co-workers (Iansek et al., 2006; Chee et al., 2009) proposed hypokinetic gait in interaction with the sequence effect as a key basal ganglia influence on FOG. Second and similar to gait, freezing phenomena, irrespective of the effectors involved, proved to be under influence of how patients deal with cognitive load embedded in the motor task. Besides setting up and maintaining a selected motor plan, associative (cognitive) and limbic commands are processed through parallel, spatially segregated loops in the BG and beyond (see Obeso et al., 2008 for review).

Typically, dopaminergic depletion first affects the posterior part of the putamen and this explains why early PD is mostly characterized by motor symptoms. The associative striatum is comparatively spared and forces patients into an increased reliance on an attention-controlled mode of behavior that would otherwise be performed automatically (Redgrave et al., 2010). Importantly, dopaminergic dysfunction in PD appears to reduce the degree of spatial segregation of BG loops (Helmich et al., 2010; Bronfeld and Bar-Gad, 2011) leading to an increased infiltration (cross-over) of non-motor information in the generation of motor output. This may improve (e.g. cueing-induced benefits (Lim et al., 2005)) or disturb performance (e.g. dual task induced worsening (Kelly et al., 2012) depending on the context (Lewis and Barker, 2009; Bronfeld and Bar-Gad, 2011) and create a neural system at risk for temporary 'jamming' of central motor-cognitive information processing as implemented in the neural reserve hypothesis (interference model) (Lewis and Barker, 2009; Shine et al., 2013d).

Based on the comparison between patients with and without FOG, functional and structural differences were found in BG structures as well as in their cortical and brainstem connection areas (Bartels and Leenders, 2008; Bartels et al., 2006; Kostic et al., 2012; Matsui et al., 2005; Tessitore et al., 2012a; Tessitore et al., 2012b; Schweder et al., 2010; Snijders et al., 2011). However, due to practical limitations of the neuroimaging environment, none of these studies directly addressed neural mechanisms during actual gait control. Therefore numerous functional neuroimaging studies (see Table 6) have recently measured brain activation in patients with and without FOG during the performance of a freezing-provoking lower limb (VR task) and upper limb (finger tapping) task.

Insert **Table 6** about here
Overview of fMRI studies using non-gait freezing paradigms

Using the VR paradigm of lower limb freezing in an fMRI context, Shine et al. were the first to investigate the neural correlates of altered motor-cognitive processing in PD with FOG and of actual freezing episodes (Shine et al., 2013a; 2013b; 2013c). In one study, patients with FOG showed reduced recruitment of cortical and subcortical areas in the cognitive control network when attempting to maintain motor output in the face of incongruent cognitive cues (Shine et al., 2013b). In these challenging dual task conditions, all patients with FOG suffered from freezing episodes which were associated with decreased activation in sensorimotor and BG regions (Shine et al., 2013a). In contrast, frontoparietal activation was higher during freezing episodes compared to successful

movement. Network analysis (Shine et al., 2013c) strengthened these findings by showing impaired dynamic coordination of motor and cognitive brain networks related to freezing. Functional connectivity (i.e. the strength of co-activation patterns between functionally coordinated neural networks) between BG, motor and cognitive control networks was reduced in PD with FOG. Most importantly, BG-cognitive network connectivity was already decreased during pre-freezing movement cycles and increased when normal movement was regained after the freeze.

The fMRI study of Vercruysse et al. (2013) also revealed a BG-cortical mismatch related to freezing in a finger repetitive movement paradigm. Brain activation patterns in both motor as well as cognitive control regions differentiated patients with FOG from those without FOG and differed between successful and frozen upper limb movement. The reversal of the pattern of increased and decreased activations in the frontostriatal areas suggested that PD with FOG showed belated neural compensation, i.e. cortical activation only increased when freezing had occurred. The finger tapping paradigm used in this study provoked freezing through increased motor load (higher frequency, smaller amplitude, more complex coordination) rather than cognitive interference as inherent to the VR tasks. Moreover, the VR task includes an element of forward walking which, even when internally represented or imagined was found to engage a basic locomotor and postural network (Zwergal et al., 2012). These paradigm differences may explain why some disparate results were found, including brainstem activation patterns related to lower limb (VR) freezing, but not to upper limb freezing.

Taken together, these non-gait freezing paradigms, although quite different in their way to experimentally trigger freezing, provide strong support for disturbed balance between BG and cortical motor-cognitive networks as a key mechanism of freezing in PD.

4. Conclusion and future directions

The above review of the literature supports the existence of a close link between FOG and non-gait freezing phenomena even though these do not capture the full complexity of FOG. We found converging evidence for the occurrence of freezing-like motor blocks during lower limb, upper limb and speech control, which present with a similar clinical manifestation as gait freezing. These types of freezing seemed to be elicited by similar spatiotemporal motor constraints that fit well with the Threshold and Decoupling models of FOG. Cognitive features of upper and lower limb freezing are in line with the Cognitive and Interference models of FOG but merit further study in relation to speech freezing. The generic nature of the various types of freezing would imply partially overlapping neural circuitry. Neuroimaging studies of upper and lower limb freezing so far suggest that both FOG and non-gait freezing are related to profound alterations in the frontostriatal circuitry in keeping with the idea of competing neural resources that interfere with ongoing motor output. Future study using complementary neuroimaging techniques such as electroencephalography (EEG) and near-infrared spectroscopy (NIRS) which offer the advantage of being able to measuring brain activation during both actual gait (and FOG) and during other non-gait and speech tasks should confirm and elaborate upon these findings (e.g. Handojoseno et al., 2013). Finally, longitudinal studies investigating multiple types of freezing in a single population are now undertaken to clear the way for a better understanding and treatment of the freezing phenomenon.

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Tables (see separate documents)

Table legends

Table 1:
Overview of the studies published between 2000 and 2013 that investigated episodic motor phenomena during lower limb movements in Parkinson's disease patients, including the proposed model(s) of freezing of gait that best match their findings.
NOTE: PD = Parkinson's disease; FOG = freezing of gait; PD+FOG = Parkinson's disease patients with freezing of gait; PD-FOG = Parkinson's disease patients without freezing of gait; CTRL = Control subjects; *(off)* = tested whilst off dopaminergic medication; *(on)* = tested whilst on regular dopaminergic medication; *(on+off)* = tested twice, once on and once off dopaminergic medication; Decoupling model = Jacobs et al. 2009, Treshold model = Plotnik et al. 2012, Interference model = Lewis and Barker 2009, Cognitive model = Vandenbossche et al. 2012.

Table 2:
Illustrations and associated descriptions of the kinematic data from studies published between 2000 and 2013 that show freezing or freezing-like phenomena in the lower limbs whilst PD patients perform various tasks that utilized diverse kinematic measures. Permission for the use of these figures was obtained from the corresponding authors of the published articles, except for references indicated by *for which we await their response.

Table 3:
Overview of the studies published between 2000 and 2013 that investigated episodic motor phenomena during upper limb movements in Parkinson's disease patients, including the proposed model(s) of freezing of gait that best match their findings.
NOTE: PD = Parkinson's disease; FOG= freezing of gait; PD+FOG= Parkinson's disease patients with freezing of gait; PD-FOG = Parkinson's disease patients without freezing of gait; CTRL = Control subjects; IP = in-phase; AP = anti-phase; *(off)* = tested whilst off dopaminergic medication; *(on)* = tested whilst on regular dopaminergic medication; *(on+off)* = tested twice, once on and once off dopaminergic medication; comf.= comfortable; ISI= inter-stimulus interval; Decoupling model = Jacobs et al. 2009, Treshold model = Plotnik et al. 2012, Interference model = Lewis and Barker 2009, Cognitive model = Vandenbossche et al. 2012.

Table 4:
Illustrations and associated descriptions of the kinematic data from studies published between 2000 and 2013 that show freezing or freezing-like phenomena in the upper limbs whilst PD patients perform various tasks that utilized diverse kinematic measures. Permission for the use of these figures was obtained from the corresponding authors of the published articles, except for references indicated by *for which we await their response.

Table 5:

Overview of the studies published between 2000 and 2013 that investigated episodic motor phenomena during speech in Parkinson's disease patients, including the proposed model(s) of freezing of gait that best match their findings.
NOTE: PD = Parkinson's disease; FOG = freezing of gait; PD+FOG = Parkinson's disease patients with freezing of gait; PD-FOG = Parkinson's disease patients without freezing of gait; CTRL = Control subjects; *(off)* = tested whilst off dopaminergic medication; *(on)* = tested whilst on regular dopaminergic medication; *(on+off)* = tested twice, once on and once off dopaminergic medication; STN-DBS = tested whilst on deep brain stimulation of the Subthalamic Nucleus; comf.= comfortable; Decoupling model = Jacobs et al. 2009, Treshold model = Plotnik et al. 2012, Interference model = Lewis and Barker 2009, Cognitive model = Vandenbossche et al. 2012.

Table 6:
Overview of functional magnetic resonance imaging (fMRI) studies that examined the neural correlates of lower limb and upper limb freezing in relation to freezing of gait (FOG).
NOTE: PD = Parkinson's disease; PD+FOG = Parkinson's disease patients with freezing of gait; PD-FOG = Parkinson's disease patients without freezing of gait; CTRL = Control subjects; *(off)* = tested whilst off dopaminergic medication; *(on)* = tested whilst on regular dopaminergic medication; *(on+off)* = tested twice, once on and once off dopaminergic medication; BOLD signal= blood oxygen level dependent signal; FC= functional connectivity; SMA= supplementary motor area; GPi= internal part of the globus pallidus; STN= subthalamic nucleus; (d)PMC= (dorsal) premotor cortex; M1= primary motor cortex; PFC= prefrontal cortex.

Table 1

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EPISODIC MOTOR DEFICITS IN LOWER LIMB MOVEMENTS						
Reference	**Groups**	**Motor task**	**Triggers**	**Motor phenomenon**	**Relation with FOG**	**Relation with FOG models**
Abe et al. (2003)	27 PD 4 CTRL *(on+off)*	**Pedaling motion** Bilateral Without cue	No manipulations	Sudden cessations	Mostly in PD+FOG	Threshold model (sequence maintenance)
Nantel et al. (2011)	15 PD+FOG 15 PD-FOG 9 CTRL *(off)*	**Stepping in place** Bilateral Without cue	No manipulations (comf. speed)	Freezing	More frequent in PD+ vs – FOG, identified gait freezers and correlated to FOG-Q PD+FOG higher asymmetry & rhythm variability	Decoupling model (weight shifting)
Nantel et al. (2012)	18 PD+FOG 11 PD-FOG *(off)*	**Stepping in place** Bilateral Without cue	No manipulations (comf. speed)	Freezing	More frequent in PD+ vs – FOG, correlated to FOG-Q and cognitive deficits PD+FOG higher asymmetry and rhythm variability	Decoupling model (weight shifting)
Vercruysse et al. (2012a)	11 PD+FOG 12 PD-FOG 11 CTRL (*off*)	**Alternating foot motion** Bilateral Without cue	No manipulations (comf. speed and amplitude)	Freezing	More frequent in PD+ vs – FOG and correlated to FOG-Q, not to cognitive scores	Threshold model (sequence maintenance)
Vercruysse et al. (2012c)	23 PD+FOG 24 PD-FOG (*on*) (*definite freezers*)	**Questionnaire** (functional LL tasks)	No manipulations	Freezing	More frequent in PD+ vs – FOG and predicted FOG	/
Gilat et al. (2013)	17 PD+FOG 11 PD-FOG *(on+off)*	**VR stepping movements** Bilateral Without cue	No manipulations (speed ~gait speed, +/-2Hz)	Freezing	Time spent freezing higher in PD+ vs -FOG in off and similar pre-freezing abnormalities PD+FOG higher step time variability vs PD-FOG in off	Threshold model (sequence maintenance)
Matar et al. (2013)	36 PD+FOG 37 PD-FOG 18 CTRL	**VR stepping movements** Bilateral Without cue	VISUOMOTOR Doorway passage (wide, narrow, sliding)	Freezing (Footstep latencies)	More freezing after conflicting cues, narrow/sliding doors in PD+	Threshold model (motor constraints) Interference model (dual task) Cognitive model (response conflict)

	(on)		COGNITIVE Stroop-like word cues (with or without implicit response conflict)		vs –FOG and correlated to FOG-Q	
Shine et al. (2013a)	24 PD+FOG 14 PD-FOG *(off)* *(definite freezers)*	**VR stepping movements** Bilateral Without cue	VISUOMOTOR Doorway passage (wide, narrow, sliding) COGNITIVE Stroop-like word cues (congruent / incongruent)	Freezing (Footstep latencies)	More freezing in PD+ vs –FOG and FOG during TUG assessment, not to FOG-Q	Threshold model (motor constraints) Interference model (dual task) Cognitive model (response conflict)

Table 2

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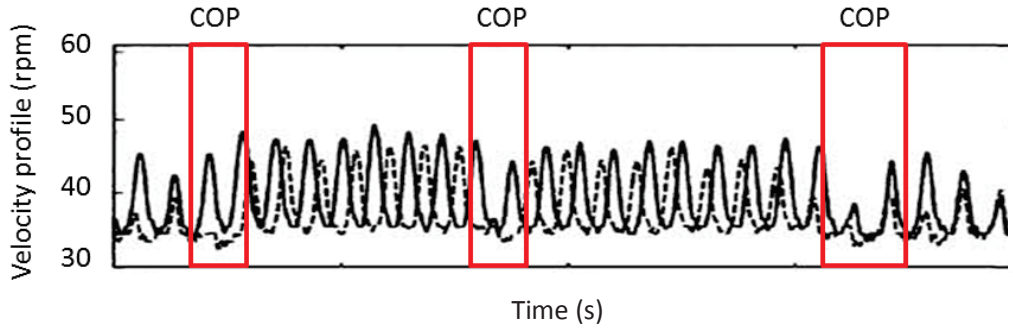
Illustrations of lower limb freezing phenomena

Abe et al. (2003)*

'Rotational velocity measures show abnormal interlimb coordination patterns during bilateral pedaling motions with sudden cessations of pedaling (COP) in PD patients with the freezing phenomenon. The dotted line represents the most affected side'

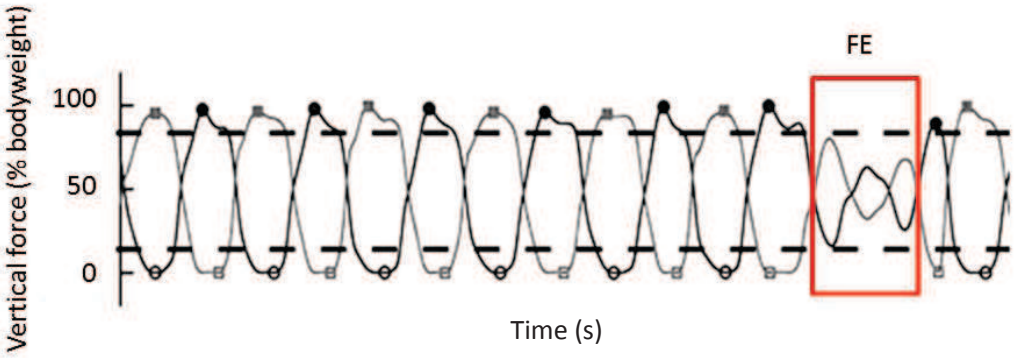
Cessations of pedaling (COP) during bilateral pedaling motions **A**



Nantel et al. (2011)

'Ground reaction forces during a stepping in place task where a freezing episode (FE) was defined as the period when a patient was unable to completely lift the foot from the force plate; i.e. when the vertical forces did not reach 100% (foot in stance) and 0% (lifting phase)'

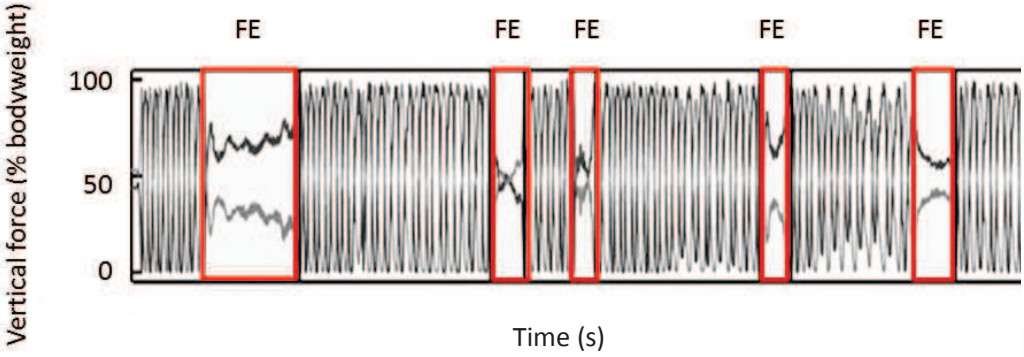
Freezing episodes (FE) during a stepping in place task **B**



Nantel et al. (2012)

'Ground reaction forces during a stepping in place task where a freezing episode (FE) was defined as the period when a patient was unable to completely lift the foot from the force plate; i.e. when the vertical forces did not reach 100% (foot in stance) and 0% (lifting phase)'

Freezing episodes (FE) during a stepping in place task **C**



Shine et al. (unpublished data)

'Vertical linear acceleration traces of the left leg during bilateral foot pedal depressions show freezing with trembling in place and a good recovery of amplitude following the freeze. A footstep latency greater than twice the modal footstep latency was defined as freezing in the virtual reality (VR) environment'

Freezing during bilateral foot movements using foot pedals in a VR environment **D**

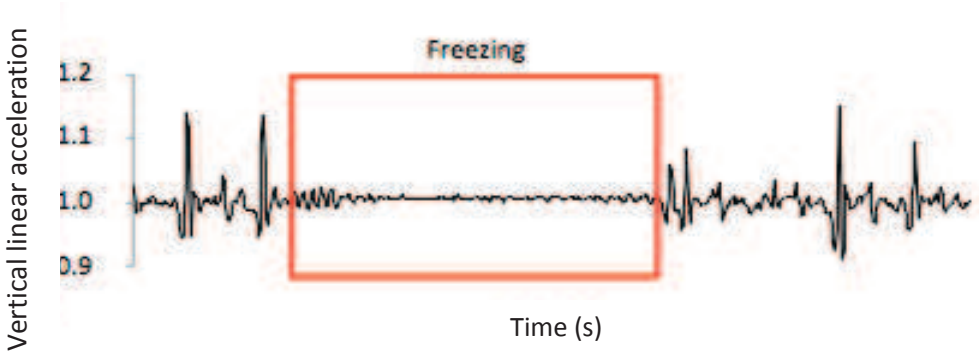


Table 3

Click here to download Table(s): Table 3_upper limb freezing descriptions_final.docx

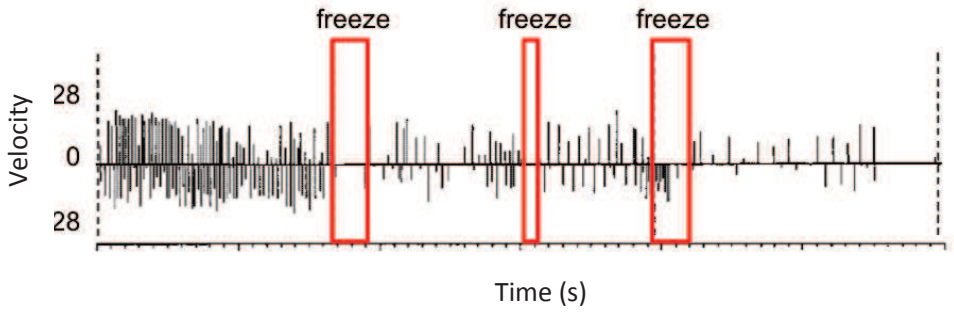
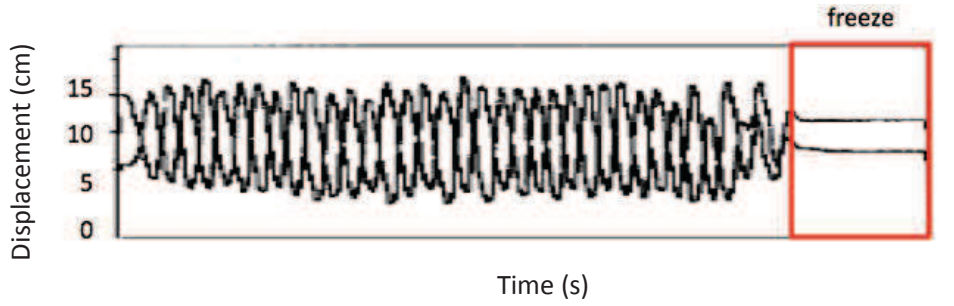
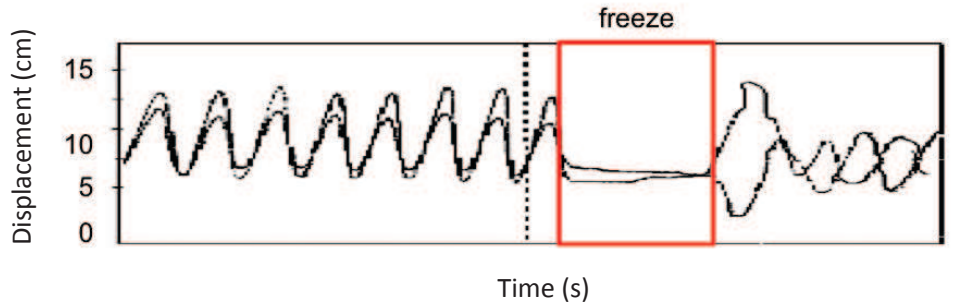
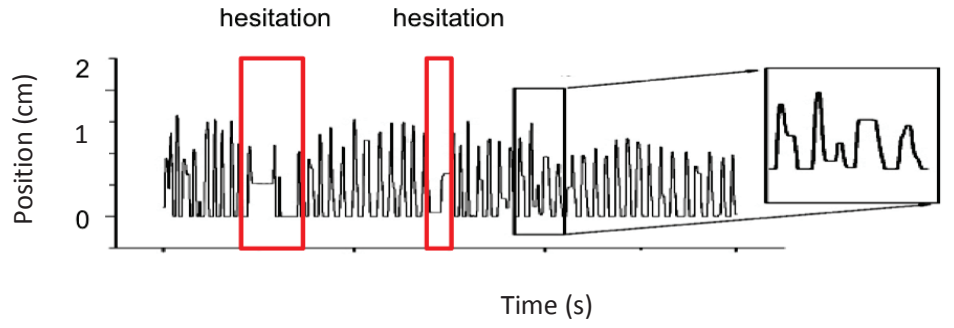
EPISODIC MOTOR DEFICITS IN UPPER LIMB MOVEMENTS						
Reference	**Groups**	**Motor task**	**Triggers**	**Motor phenomenon**	**Relation with FOG**	**Relation with FOG models**
Bronte-Stewart et al. (2000)	16 PD 11 CTRL *(on+off)*	**Finger tapping** Unilateral Without cue	MOTOR Speed (max.)	Freezing Festination Start akinesia	Discussed in relation to gait freezing and festination	Threshold model (motor constraints) Decoupling model (initiation freeze)
Almeida et al. (2002)	13 PD 13 CTRL (*on*)	**Hand drawing** Bilateral With & without cue	MOTOR Speed (0.75-1.25-1.75Hz) Pattern (IP/AP)	Freezing	not explored	Threshold model (motor constraints)
Almeida et al. (2003)	13 PD 13 CTRL (*on*)	**Hand drawing** Bilateral With & without cue	MOTOR Speed (0.75-1.25-1.75Hz) MOTOR-COGNITIVE Pattern switch (IP/AP)	Freezing Initiation freeze	not explored	Threshold model (motor constraints) Decoupling model (initiation freeze) Cognitive model (response conflict after switch)
Yahalom et al. (2004)	51 PD 36 CTRL (*on*)	**Hand tapping** Unilateral, dominant hand With cue	MOTOR Speed (comf., max., 2-5Hz)	Hastening	More frequent in tremor-dominant vs freezing-dominant PD	Threshold model (motor constraints)
Sauermann et al. (2005)	15 PD 6 CTRL (*on*)	**Thumb flexion/extension** Unilateral, both hands Without cue	MOTOR Speed (max.) Amplitude (max.)	Hand akinesia Hesitations	Not explored	Threshold model (motor constraints)
Moreau et al. (2007)	31 PD+FOG 9 PD-FOG 20 CTRL *(off)* (FOG/Festination)	**Finger tapping** Bilateral Without cue	No manipulations Speed (comf.)	Motor blocks Hastening	More frequent in PD+FOG/festination vs those without	Threshold model (sequence maintenance)
Popovic et al. (2008)	8 PD (*on*)	**Hand pointing** Unilateral	No manipulations	Motor blocks	Not explored	Threshold model (sequence maintenance)
Nieuwboer et al. (2009)	10 PD+FOG 10 PD-FOG 5 CTRL (*off*)	**Hand writing** Bilateral With & without cue	MOTOR Speed (comf., max.) Amplitude (large, small)	Freezing	More frequent in PD+FOG and correlated to FOG-Q	Threshold model (motor constraints)
Stegemöller et al. (2009)	9 PD 9 CTRL	**Finger tapping** Unilateral, dominant hand	MOTOR Speed (1-3Hz)	Movement breakdown	Not explored	Threshold model (motor constraints)

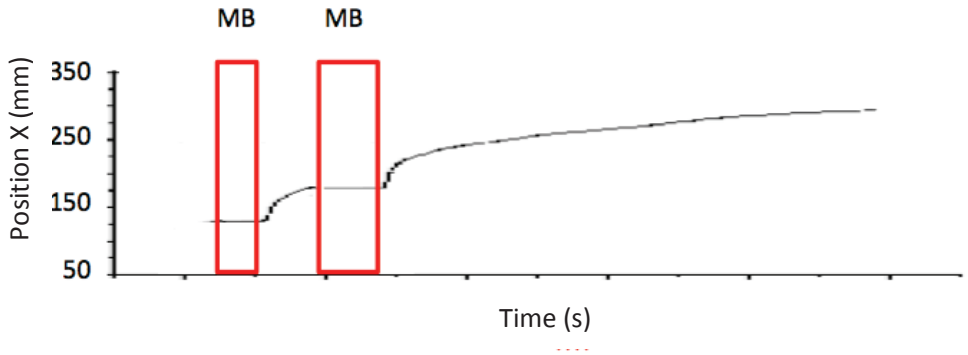
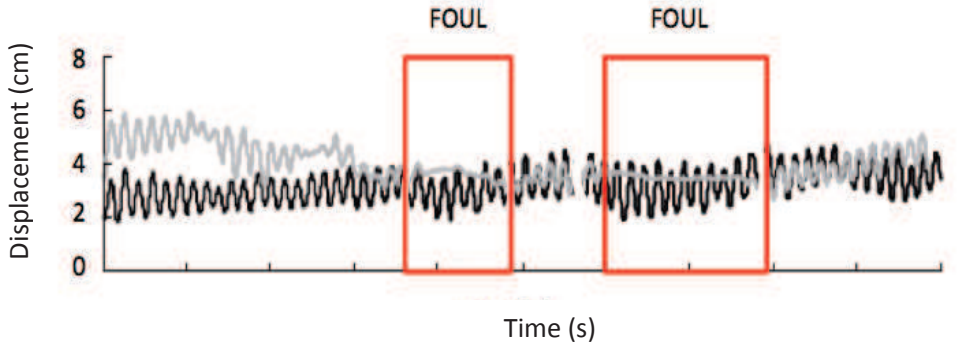
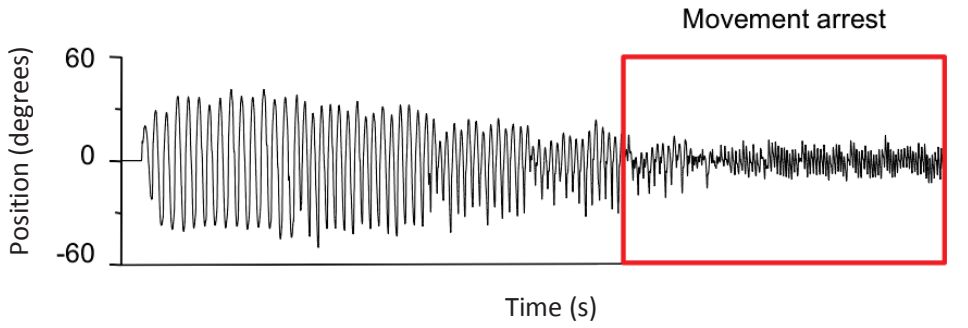
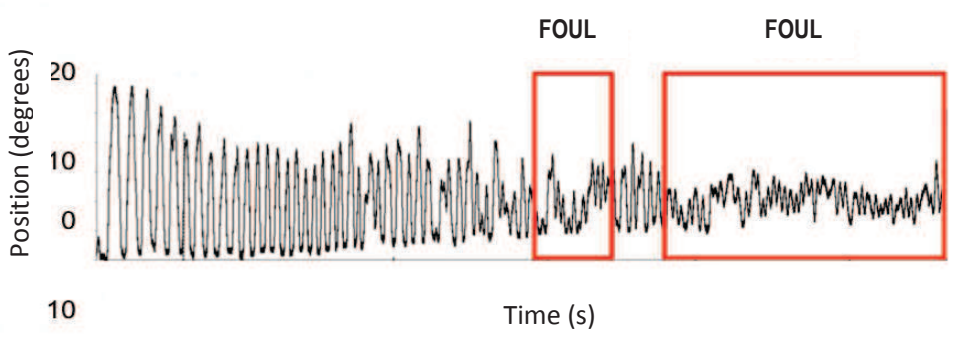
	(*on+off*)	With cue				
Naismith et al. (2010)	12 PD *(on)*	**Hand tapping** Bilateral Without cue	MOTOR Doorway passages COGNITIVE Stroop-like word cues	Freezing Start hesitations	Hesitations and freezing correlated to FOG-Q	Threshold model (motor constraints) Interference model (dual task) Cognitive model (response conflict) Decoupling model (initiation freeze)
Jones et al. (2011)	22 PD 20 CTRL (on+off, 8 de novo)	**Finger tapping** Unilateral, dominant hand With cue / cue withdrawal	MOTOR Speed (250-2000ms ISI)	Festination	Not explored	Threshold model (motor constraints)
Espay et al. (2012)	4 PD+FOG (*off+on+supra-on)*	**Hand pro-/ supination** Unilateral Without cue	MOTOR Speed (max.) Amplitude (max.)	Freezing	Pure ON-FOG associated with ON-UL freezing	Threshold model (motor constraints)
Vercruysse et al. (2012a ; 2012b)	11 PD+FOG 12 PD-FOG 11 CTRL (*off*)	**Finger tapping** Bilateral With cue / cue withdrawal	MOTOR Speed (comf., fast) Amplitude (comf., small) Pattern (IP, AP)	Freezing	More frequent in PD+FOG and correlated to FOG-Q	Threshold model (motor constraints) Cognitive model (cue withdrawal)
Vercruysse et al. (2012c)	23 PD+FOG 24 PD-FOG (*on*) (*definite freezers*)	**Questionnaire** (functional UL taks)	No manipulations	Freezing	More frequent in and predictor of belonging to PD+FOG	/
Williams et al. (2013)	12 PD+FOG 16 PD-FOG 19 CTRL (*off*) *(PD not mached)*	**Finger tapping** Bilateral With cue / cue withdrawal	MOTOR Speed (comf., fast) Amplitude (comf., small)	Freezing	Freezing and general coordination during SmallFast correlated to FOG-Q	Threshold model (motor constraints) Cognitive model (cue withdrawal)
Stegemöller et al. (2013)	9 PD 9 CTRL (*off, on+off STN-DBS*)	**Finger tapping** Unilateral, dominant With cue	MOTOR Speed (1-3Hz)	Hastening/ Freezing	Not explored	Threshold model (motor constraints)

Table 4

Click here to download Table(s): Table 4_upper limb freezing figures_final.docx

Illustrations of upper limb freezing phenomena

Bronte-Stewart et al. (2000) *'Velocity traces during a rapid alternating finger tapping task show festination and freezing, defined as the complete cessation of activity in one or both fingers in all kinematic variables that lasted longer than the mean interval between finger strikes of the preceding 5 seconds plus two standard deviations'*	**Freezing during rapid alternating finger tapping** **A** 
Almeida et al. (2002) *'Relative phase between upper limbs during continues anti-phase displacements of two linear sliding devices in a parallel plane to the body at 1.75 Hz. A freeze was defined as a 1-second period, within a trial, in which no change in movement amplitude was observed in either one or both of the limbs'*	**Freezing during a bimanual sliding task** **B** 
Almeida et al. (2003) *'Relative phase between upper limbs during continues displacement of two linear sliding devices in a plane parallel to the body with a task to switch from in-phase to anti-phase movements. A freeze was defined as any period of at least 1s in which one, or both of the limbs displayed no movement (zero change in amplitude)'*	**Freezing during a bimanual sliding task** **C** 
Sauermann et al. (2005)* *'Position data of PD patients that repeatedly depressed a push button with the thumb (i.e. flexion and extension) within a range of 2cm showed unsteady movements with lower frequency and amplitude that included multiple interruptions in the flexing and extension movements (hesitation), compared to controls'*	**Hesitations during repeated thumb flexion and extension movements** **D** 

Popovic et al. (2008) *'Position data of PD patients during volitional point-to-point hand movements on a drawing tablet using a computer mouse showed sudden non-volitional discontinuations of motor activity, called motor blocks (MB) or freezing'*	**Motor blocks (MB) during a volitional planar movement pointing task** **E** 
Nieuwboer et al. (2009) *'Position data of PD patients with freezing during a repetitive drawing task in an anti-phase pattern on a digitizer tablet showed freezing of the upper limbs (FOUL), which were defined as a period lasting more than 1 s in which one or both limbs displayed no movement, preceded by reductions of amplitude and/or increased or irregular cycling frequency'*	**Freezing during alternating writing motion** **F** 
Stegemöller et al. (2009) *'Position data of PD patients that synchronized the flexion/extension of their index finger to an auditory tone show marked deterioration of movement performance (i.e. decreased amplitude, increased frequency and loss of phase) when auditory tone frequency increased to 2Hz, which may be analogous to movement arrest'*	**Movement arrest during unilateral finger tapping** **G** 
Vercruysse et al. (2012a) *'Position data of PD patients with FOG that performed internally generated rhythmic bilateral finger movements show freezing of the upper limbs (FOUL), a period of involuntary stop or clear absence of effective cyclic movements with strong amplitude decline and frequency increase prior to the freezing episode'*	**Freezing of the upper limbs (FO-UL) during bilateral finger tapping** **H** 

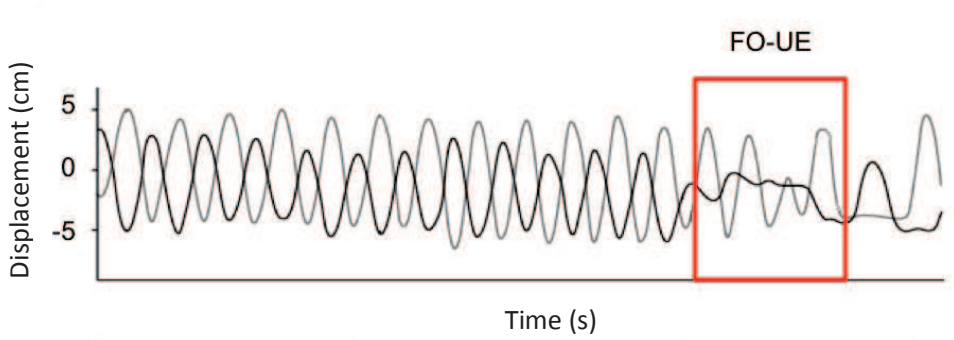
Williams et al. (2013) *'Position data of PD patients performing rhythmical upper extremity movements show freezing of the upper extremities (FO-UE), defined as a sudden halt or decrease in amplitude of movement deviated from the duration and amplitude of an average movement cycle'*	**Freezing during bilateral finger tapping** **I** 

Table 5

Click here to download Table(s): Table 5_speech freezing descriptions.docx

EPISODIC MOTOR DEFICITS DURING SPEECH						
Reference	**Groups**	**Motor task**	**Triggers**	**Motor phenomenon**	**Relation with FOG**	**Relation with FOG models**
Giladi et al. (2001)	800 PD *(baseline)*	**UPDRS & ADL scores**	No manipulations	Palilalia Tachyphemia Tip-of-the-tongue phen. Speech freezing	Speech abnormalities associated with FOG development longitudinally	Threshold model (articulatory coordination) Cognitive model (tip-of-the tongue)
Moreau et al. (2007)	31 PD+FOG 9 PD-FOG 20 CTRL *(off)*	**Diadochokinesis task** With cue	MOTOR Speed (1-7Hz)	Frequency breakdown Oral festination (OF)	Frequency breakdown in PD with FOG OF more frequent in PD with gait freezing and festination, not in isolated FOG	Threshold model (motor constraints)
Cantiniaux et al. (2010)	11 PD 11 CTRL *(on+off med/STN-DBS)*	**Reading out loud** Without cue	MOTOR Speed (slow, comf., max.)	Speech akinesia	'Resembles gait akinesia' (reduced step length)	Threshold model (motor constraints)
Vercruysse et al. (2012c)	23 PD+FOG 24 PD-FOG (*on*) (*definite freezers*)	**Questionnaire** (daily speech)	No manipulations	Speech freezing	More frequent in and predictor of belonging to PD+FOG	/
Park et al. (2013)	9 PD+FOG 9 PD-FOG *(off)*	**Reading out loud** With/without cues	MOTOR Mono/polysyllabic words	Sever dysfluency	More frequent in PD+FOG Correlated cue-effects on speech and gait only in PD+FOG	Threshold model (motor constraints)

Table 6

Click here to download Table(s): Table 6_fMRI studies on non-gait freezing.docx

FUNCTIONAL NEUROIMAGING STUDIES ON NON-GAIT FREEZING				
Reference	**Groups**	**Motor paradigm**	**Neural outcome**	**Main results**
Shine et al. (2013b)	14 PD+FOG 15 PD-FOG (*off*) (confirmed FOG)	Lower limb (LL) VR stepping task	Task-related BOLD signal (fMRI)	**Continuous motor-cognitive processing in PD+FOG vs. PD-FOG** Decreased BOLD in cortical areas (anterior insula, preSMA) Decreased BOLD in BG (ventral striatum, STN)
Shine et al. (2013a)	18 PD+FOG (*off*) (confirmed FOG)	Lower limb (LL) VR stepping task	Task-related BOLD signal (fMRI)	**Episodic breakdown (LL freezing) vs. continuous movement** Decreased BOLD in cortical sensorimotor regions Decreased BOLD in BG (caudate, GPi, STN) Increased BOLD in cortical frontoparietal regions
Shine et al. (2013c)	10 PD+FOG 10 PD-FOG (on + *off*) (confirmed FOG)	Lower limb (LL) VR stepping task	Task-related network activity (~BOLD) Task-related functional connectivity (FC) (fMRI)	**Continuous motor-cognitive processing in in PD+FOG vs. PD-FOG** Decreased activity in motor, BG and ventral attention (only in *off*) networks **Episodic breakdown (LL freezing) vs. continuous movement** Decreased FC between right cognitive control network and BG network
Vercruysse et al. (2013)	16 PD+FOG 16 PD-FOG 16 CTRL (*off*)	Upper limb (UL) Finger tapping task	Task-related BOLD signal (fMRI)	**Continuous motor processing in PD+FOG vs. PD-FOG and CTRLS** Decreased BOLD in cortical frontal areas (dPMC, M1, PFC) Increased BOLD in BG (putamen, pallidum, STN) **Episodic breakdown (UL freezing) vs. continuous movement** Increased BOLD in cortical areas (SMA, M1, PMC, PFC) Decreased BOLD in BG (putamen, pallidum)